Group 2 Patients
Neutralising Monoclonal Antibodies and Antivirals for patients *with hospital-onset* COVID-19
Guidance for use in GGC

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Introduction

Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2. Neutralising monoclonal antibodies (nMAB) bind to specific sites on the spike protein of the SARS-CoV-2 virus particle, blocking its entry into cells and therefore inhibiting its replication.

Recent evidence suggests that antivirals and nMABs given early in the course of infection significantly improve clinical outcomes in patients with COVID-19 who are at high risk of progression to severe disease and/or death. Key findings are as follows:

- Paxlovid™ (PF-07321332 (nirmatrelvir) plus ritonavir)- administered orally as dual antiviral treatment in the EPIC HR trial resulted in a relative risk reduction of hospitalisation or death by 89% (within 3 days of symptom onset) and 88% (within 5 days of symptom onset) compared to placebo in non-hospitalised, high-risk adults with COVID-19. (Pfizer press release).
- Remdesivir administered intravenously over 3 days to non-hospitalised patients within 7 days of COVID-19 symptom onset and had risk factors for disease progression, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb et al, 2021).
- Sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression resulted in a relative risk reduction in hospitalisation or death at day 29 by 85% in the interim analysis of the COMET-ICE trial (Gupta et al, 2021a). Final analysis of this trial shows a relative risk reduction of 79% (Gupta et al, 2021b).

The above products have a conditional marketing authorisations for use in the treatment of COVID-19 in the UK as follows.

- Paxlovid™ for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.
- Remdesivir for:
    - the treatment of COVID-19 in adults and adolescents (aged 12 years and over and weighing at least 40kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5 days. Up to 10 days treatment may be offered to severely immunocompromised patients.
    - the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 within 7 days of symptom onset, for a treatment duration of 3 days.
- Sotrovimab (Xevudy™) for the treatment of symptomatic adults, and adolescents (aged 12 years and over and weighing at least 40kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection.

The decision to initiate antiviral or nMAB must be made by a Consultant and be within the defined criteria.

If a patient does not meet the eligibility criteria and antiviral or nMAB therapy is still felt to be a therapeutic consideration, the Consultant in charge of the patient's care must discuss the case with at least one other Consultant who has expertise in the management of COVID, for example the on call Infectious Diseases or Respiratory Consultant. It may be that a broader MDT discussion is required in complex cases. The summary and outcome of this discussion, along with the names of the clinicians involved in the discussion, must be clearly documented in a clinical note on Portal.

Group 2 Eligibility Criteria

Hospitalised patients (aged 12 and above) with onset of COVID-19 are eligible to be considered for treatment with nMAB or antiviral medicines if:

- They are hospitalised for indications other than for the management of acute symptoms of COVID-19 (including patients admitted to community and mental health hospitals. Where possible patients being considered for intravenous treatment should be transferred to a suitable facility for treatment delivery.)

AND

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or lateral flow test (a confirmatory PCR test is recommended to support surveillance activities),

AND

- Symptomatic with COVID-19 and showing no signs of clinical recovery.
    - The following are considered symptoms of COVID-19: feverish, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhoea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach ache, rash, sneezing, sputum or phlegm, runny nose.
    - For patients who have been symptomatic (within the specified time period) but are no longer symptomatic, clinical judgement should determine suitability for treatment.

AND

- They are a member of a member of a 'highest' risk group (as defined in Appendix 1) **OR,** COVID-19 infection presents a material risk of destabilising a pre-existing condition* or illness* or compromising recovery from surgery or other hospital procedure (as determined by multidisciplinary team [MDT] assessment)

*In addition to Appendix 1, conditions at risk of progression to severe disease include, but are not limited to the following: elderly, frail, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (body mass index [BMI] ≥30 kg/m^2).

Children aged 12-17 years in Group 2 may only be considered for treatment with remdesivir (this is off-label under this policy) or sotrovimab. For paediatric/adolescent patients (aged 12-16 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

Available treatment options for eligible patients are:

- **First-line**: Paxlovid™ (PF-07321332 (nirmatrelvir) plus ritonavir) (antiviral)
- **Second-line**: Remdesivir (antiviral) or sotrovimab (nMAB)

Please see appendix 3 for guidance on selection of treatment.

Please note:

- there are no clinical data to support the above therapies for patients who test positive but are asymptomatic.
- Combination treatment with an nMAB and an antiviral is NOT routinely recommended.
- Retreatment of recurrent or prolonged infections in an individual patient must be discussed with one of the ID Consultants in normal working hours.
- Paxlovid has significant drug interactions – the interaction checker must be used before prescribing this medication

Group 2 Exclusion Criteria

The following patients are not eligible for treatment in Group 2:

- The pattern of clinical presentation indicates that there is recovery rather than risk of deterioration from infection
- Require hospitalisation specifically for the management of acute COVID-19 illness
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms
- Children and adolescents (12-17) weighing less than 40kg
- Children aged under 12 years
- Known hypersensitivity reaction to the active substances or to any of the excipients of the products as listed in the respective Summary of Product Characteristics (SmPC)..

Paxlovid™ (PF-07321332 (nirmatrelvir) plus ritonavir) Eligibility Criteria

If the general criteria above are met, patients may be considered for treatment with Paxlovid™ if:

- Treatment is commenced within 7 days of symptom onset*
  AND
- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease (eGFR <30ml/min)
  AND
- Paxlovid™ treatment has been deemed safe following guidance from the appropriate specialty team(s) – see Appendix 3 for NHS GGC Inpatient Pathway and Prescribing Guide. The accompanying National Clinical Guide for treatment with antivirals and nMABs is available at https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103192

Paxlovid™ Additional Exclusion Criteria

- Children aged less than 18 years
- Pregnancy or breastfeeding
- The patient is taking any of the medications listed in Appendix 3. Please contact pharmacy teams if further advice on potential interactions are required or check https://www.covid19-druginteractions.org/checker.

Paxlovid™ Cautions

Paxlovid™ is not recommended for the treatment of patients with advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease who are not hospitalised.

Dose modification in stage 3 chronic kidney disease (eGFR 30-59ml/min) is recommended as per the SmPC – please see dosing section below.

Please refer to the SmPC for Paxlovid™ for detail on special warnings and precautions for use.

Paxlovid™ has a risk of serious adverse reactions due to interactions with other medicinal products (see Appendix 3 for prescribing guidance).

Initiation of Paxlovid™, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving Paxlovid™, may increase plasma concentrations of medicinal products metabolised by CYP3A. Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid™, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of Paxlovid™.
- Loss of therapeutic effect of Paxlovid™ and possible development of viral resistance.

Remdesivir

If the general criteria above are met, patients may be considered for treatment with remdesivir if:

- Treatment with Paxlovid™ is contraindicated or not possible
  AND
- Treatment is commenced within 7 days of symptom onset

Remdesivir Exclusion Criteria

- As noted above for Group 2 Exclusion Criteria plus:
  - eGFR <30ml/min,
  - ALT>5x ULN

Remdesivir Cautions

Please refer to the SmPC for remdesivir for special warnings and precautions for use. Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate.

Sotrovimab Eligibility Criteria

If the general criteria above are met, patients may be considered for treatment with sotrovimab if:

- Clinical judgement deems that an nMAB is the preferred option
  OR
- Treatment with remdesivir and Paxlovid™ are both contraindicated or not possible
  AND
- Treatment is commenced within 7 days of symptom onset*

Sotrovimab Additional Exclusion Criteria

- As noted above for Group 2 Exclusion Criteria.

Where possible, all patients being considered for treatment with sotrovimab should have samples taken for serology testing against SARS-CoV-2 prior to treatment. However, serology results are **not** a requirement for treatment with nMABs under the criteria specified in this policy.

Patients who have received an nMAB within a post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) trial (such as the PROTECT-V trial) who meet the eligibility criteria of this policy can still receive treatment with sotrovimab, if this is deemed the most appropriate treatment option

Sotrovimab Cautions

Please refer to the SmPC for sotrovimab for special warnings and precautions for use.

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. These reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing.

If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated.

If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered.

The nMAB therapy is not intended to be used as a substitute for vaccination against COVID-19.

***Please note treatment commencement for Paxlovid™ and sotrovimab beyond 5 days from symptom onset is off-label.**

Paxlovid™ Dosing & Administration

The recommended dose of Paxlovid™ (PF-07321332 (nirmatrelvir) plus ritonavir) is

- 300mg (two 150mg tablets) PF-07321332 (may also be known as nirmatrelvir) with
- 100mg (one 100mg tablet) ritonavir taken together **orally twice daily for 5 days only**. Treatment must not be extended beyond 5 days.

Dose Reduction Stage 3 Chronic Kidney Disease (eGFR 30-59ml/min)

The recommended dose of Paxlovid™ (PF-07321332 (nirmatrelvir) plus ritonavir) is

- 150mg (one 150mg tablet) PF-07321332 (may also be known as nirmatrelvir) with
- 100mg (one 100mg tablet) ritonavir taken together **orally twice daily for 5 days only**. Treatment must not be extended beyond 5 days.

The remaining tablets of PF-07321332 should be disposed of in accordance with local requirements.

Paxlovid™ should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of onset of symptoms*. Clinicians should assure themselves that patients are able to swallow the oral tablets. The tablets must not be crushed or dissolved and can only be taken orally. They may not be suitable in patients where the enteral route is compromised.

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

Remdesivir Dosing and Administration

The recommended dose of remdesivir for this cohort is:

- 200mg intravenously on day 1 followed by
- 100mg intravenously on days 2 and 3.

Please note dosing for children and adolescents (12-17) is off label for this remdesivir protocol.

Doses should be diluted in either a 250ml or 100ml pre-filled bag of 0.9% sodium chloride solution and infused over a minimum of 30 minutes.

If the patient requires low-flow supplemental oxygen they should be treated according to the UK Clinical Commissioning Policy for remdesivir for patients hospitalised with COVID-19. See GGC remdesivir treatment flowchart here.

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. **Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms.** Patients should be monitored for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, administration of remdesivir should be discontinued immediately and appropriate treatment initiated.

Sotrovimab Dosing and Administration

The recommended **dose of sotrovimab is a single 500 mg intravenous infusion** administered following dilution.

Sotrovimab must be diluted in a single 100mL bag of 0.9% sodium chloride or glucose 5% (do not require to remove an equivalent volume of saline) - total volume 108mL and given over a minimum of 30 minutes via 0.2 micron inline filter.

The SmPC refers to allowing the vials to reach room temperature before use. This is for reasons of patient comfort during administration. If the diluent bag used is at room temperature, there is no need to allow the vial to warm first.

- **Sotrovimab must not be infused concomitantly in the same intravenous line with other medication. Repeat doses should not be administered**.
- Hypersensitivity reactions, including anaphylaxis, have been reported with administration of sotrovimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.
- Infusion-related reactions (IRRs) have been observed with IV administration of sotrovimab. IRRs observed in clinical studies were mostly mild to moderate in severity. The commonly reported signs and symptoms for these reactions are nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, IRRs may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Pregnancy and Women of Childbearing Potential

Clinicians should refer to the SmPCs for the relevant products for further information on use in pregnancy and women of childbearing potential. **Paxlovid™ requires particular attention to the detail**

All healthcare professionals are asked to ensure that any patients who receive a COVID-19 antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 so that they can be followed up. For more information go to http://www.uktis.org/.

There are no human data on the use of **Paxlovid™** during pregnancy to inform the drug-associated risk of adverse developmental outcomes - women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid™. **Paxlovid™ is not recommended during pregnancy and in women of childbearing potential not using effective contraception**.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping Paxlovid™.

There are no or limited amount of data from the use of **remdesivir** in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see SmPC for further information).

There are no data from the use of **sotrovimab** in pregnant women. The SmPC for sotrovimab states that sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.
Prescribers should discuss contraception post treatment as appropriate, taking into account the ½ life of sotrovimab is ~49 days.

Fertility

There are no human data on the effect of **Paxlovid™** on fertility. No human data on the effect of PF-07321332 on fertility are available. PF-07321332 produced no effects on fertility in rats. There are no human data on the effect of **ritonavir** on fertility. Ritonavir produced no effects on fertility in rats.

No human data on the effect of **remdesivir** on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see SmPC). The relevance for humans is unknown.

There are no data on the effects of **sotrovimab** on human male or female fertility. Effects on male and female fertility have not been evaluated in animal studies.

Breast-feeding

It is unknown whether **PF-07321332** is excreted in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of **ritonavir** on the breast-fed newborn/infant or the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with **Paxlovid™** and for 7 days after the last dose of **Paxlovid™**.

It is unknown whether **remdesivir** is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given remedesivir. Therefore, excretion of remdesivir and/or metabolites into the milk of lactating animals can be assumed.

Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

There are no data on the excretion of **sotrovimab** in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known.

Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Maternal IgG is known to be present in human milk.

Co-Administration

Co-administration of **sotrovimab** and **remdesivir** with corticosteroids, and IL6-inhibitors is permitted and no drug-drug interactions are expected. **All potential interactions with Paxlovid™ must be assessed and mitigated prior to initiating treatment.**
For further information please visit the University of Liverpool COVID-19 Drug Interactions website: (https://www.covid19-druginteractions.org/checker).
Sotrovimab should not be regarded as an alternative to corticosteroids.

Other helpful information on the use of nMABs for COVID

S-Antibody Testing

The process for sending samples for S-antibody testing is as follows:

- Sample type is an SST Tube ie yellow (ochre) top tube.
- IgG Spike antibody testing is provided from the Biochemistry Department at the QEUH.
- Samples at sites other than QEUH should be sent to the local lab for forwarding to QEUH Biochemistry Dept.
- Samples will be run Mon-Fri 9am – 5pm and Sat-Sun 9am-1pm.
- Results will be provided the same day for samples received between these times. Samples received after 5pm at the QEUH will be analysed the following morning.
- Requests for this test can be made via TrakCare, the request item is **"Covid IgG Spike Protein Assay"** this will also enable results to be visible in TrakCare as well as clinical portal.
- Please note that the Abbott assay used within NHS GG&C has a different cut off to the assay result previously received via NHS Lanarkshire.
  Results <50 U/mL will be reported as 'Not-Detected' ≡ Seronegative.

Obtaining supply of Paxlovid™, Remdesivir or Sotrovimab

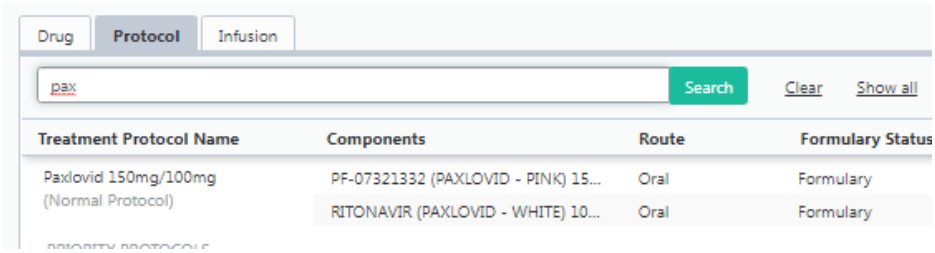
Before prescribing, patients must fulfil the criteria defined above or have approval from a locally arranged MDT if exceptionality applies. **Please ensure interactions with Paxlovid ™ have been checked and mitigated before ordering from pharmacy**.

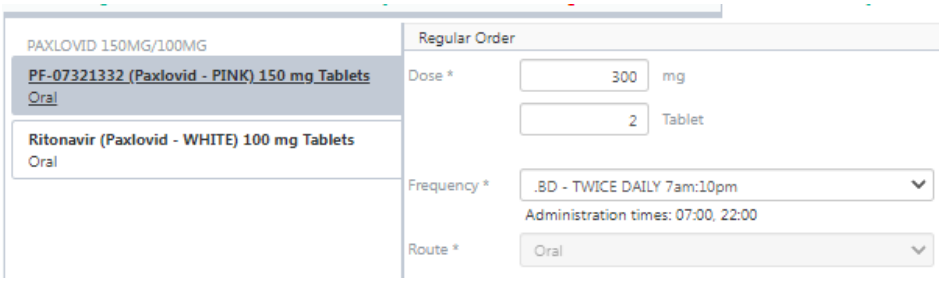
If the one of above medications is indicated, the clinical team looking after the patient should contact the ward clinical pharmacist in first instance to arrange a supply. If no ward pharmacist available, contact main pharmacy for a named-patient supply. The indent should indicate the patient ID details including CHI and which consultant has approved its use. **For Paxlovid™ ensure dose is clearly stated.** Pharmacy departments will supply the remdesivir or sotrovimab vials. For sotrovimab a 0.2 micron inline filter and a worksheet required to assemble the final infusion for administration will also be supplied. **These will be supplied on a named patient basis only during pharmacy opening hours. Please do not contact the on-call pharmacist out of hours for supply**. Sotrovimab must be stored in a fridge when not in use (do not keep inline filters in fridge). Completed worksheets should be filed in the patients notes. Paxlovid™ will be supplied labelled to enable the supply to be taken home with the patient if they are discharged before the 5 day course is complete. If a reduced dose of Paxlovid™ has been requested, supply will be made with excess tablets removed from the packaging.

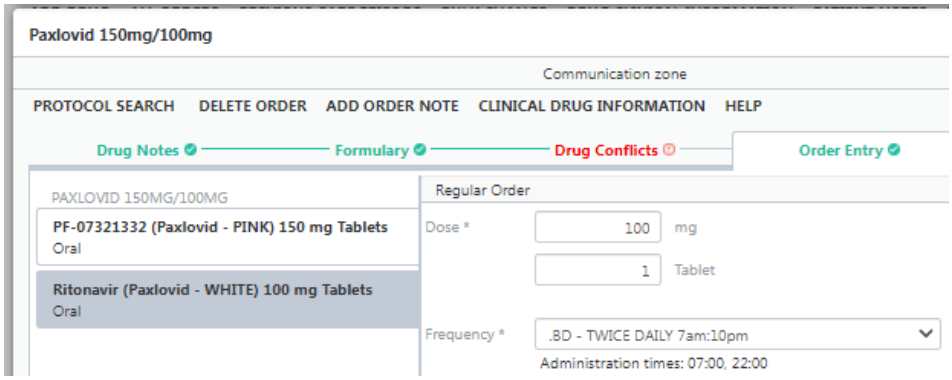
Prescribing & Administering Paxlovid™ on HEPMA

In HEPMA Paxlovid™ has been set up as a 'protocol' for prescribing rather than a 'drug' due to being two physical products that must be prescribed and administered.

Please see screenshots below for the process of selecting the protocol and prescribing (Please ensure correct dose of PF-07321332 in the case of dose reduction required).







Monitoring, tracking and follow up

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly mention the name of the treatment that has been given and the date of administration.

There is an urgent need to generate more evidence and greater understanding around the use of nMABs and antivirals in the treatment of patients with COVID-19. Both surveillance and service evaluation are necessary to gain knowledge around the following: factors of relevance in determining nMAB and antiviral treatments; the impact of nMAB and antiviral treatments in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB and antiviral use, such as generation of new mutations.

Treating clinicians are asked to ensure that all PCR tests undertaken as an inpatient and/or in the community where any patient who is receiving ongoing PCR testing as part of secondary care (for example, through an outpatient clinic) should do this through the hospital laboratories (**WoSSVC or HUB** Not Lighthouse) where these samples will be sequenced if positive– **please specify 'Post nMAB PCR' on the sample request form**.

Monitoring of longer-term progress is strongly recommended via recruitment of patients receiving COVID therapies to the ISARIC-CCP study.

Safety reporting

It is vital that any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) are reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk

COVID-19 Vaccines

The Green Book states

"Monoclonal antibodies to COVID-19 have recently been licensed for the treatment and prophylaxis of COVID-19 infection. Primate data suggests that administration of the AstraZeneca combination monoclonal antibody product did not interfere with the subsequent response to active vaccination. Based on this limited evidence, therefore, no specific interval is required between receipt of these products and COVID-19 vaccination, or vice versa. As the use of these products is likely to be prioritised to those who are less able to respond to vaccination, for example immunosuppressed individuals, additional doses of vaccine may be required as outlined above"

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040677/Greenbook-chapter-14a-14Dec21.pdf

Appendix 1

Table 1: Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs

The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC).

Cohort	Description
Down's syndrome	All patients with Down's syndrome
Patients with a solid cancer	• Active metastatic cancer and active solid cancers (at any stage) • All patients receiving chemotherapy within the last 3 months • Patients receiving group B or C chemotherapy 3-12 months prior (see Appendix 2) • Patients receiving radiotherapy within the last 6 months
Patients with a haematologic malignancy and stem cell transplant recipients	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases) • Autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases) • Individuals with haematological malignancies who have o received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or o radiotherapy in the last 6 months • Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months except patients with chronic phase chronic myeloid leukaemia (CML) in molecular response or first or second line tyrosine kinase inhibitors (TKI). • All patients with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) or myelodysplastic syndrome (MDS) who do not fit the criteria above. • All patients with sickle cell disease. • Individuals with non-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting

	systemic treatment (e.g. anti-CD20, anti-thymocyte globulin [ATG] and alemtzumab) within the last 12 months

Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who:
	  o Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin)
	  o Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals
	  o Not been vaccinated prior to transplantation
	• Non-transplant patients who have received a comparable level of immunosuppression
	• Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m^2) without immunosuppression

Patients with liver disease	• Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease). • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) • Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders (IMID)	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable disease on corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID with stable disease on either corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Primary immune deficiencies	• Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • Severe Combined Immunodeficiency (SCID)

	• Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Primary immunodeficiency associated with impaired type I interferon signalling • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias) • Any patient with a secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy.
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm^3 and stable on HIV treatment or CD4>350 cells/mm^3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	• Multiple sclerosis • Motor neurone disease • Myasthenia gravis • Huntington's disease

Appendix 2 Chemotherapy Category (Groups B and C)

Group B	Group C
10-50% risk of grade 3/4 febrile neutropenia or lymphopenia	>50% risk of grade 3/4 febrile neutropenia or lymphopenia
• Etoposide based regimens • CMF • Irinotecan and Oxaliplatin based regimens • Cabazitaxel • Gemcitabine • Chlorambucil • Temozolomide • Daratumumab • Rituximab • Obinutuzumab • Pentostatin • Proteosome inhibitors • IMIDs • PI3Kinase inhibitors • BTK inhibitors • JAK inhibitors • Venetoclax • Trastuzumab-emtansine • Anthracycline-based regimens • Fluorouracil, epirubicin and cyclophosphamide (FEC) • Methotrexate, vinblastine, adriamycin/doxorubicin, cisplatin (MVAC) • Adriamycin/doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) • Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) • Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP) • Liposomal doxorubicin • Taxane – 3-weekly • Nab-paclitaxel • Carboplatin-based regimens • Ifosphamide-based regimens • Bendamustine • Cladrabine • Topotecan • Cyclophosphamide/Fludarabine combinations	• All acute myeloid leukaemia/acute lymphocytic regimens • Bleomycin, etoposide and platinum • Highly immunosuppressive chemotherapy (e.g. FluDAP, high dose Methotrexate & Cytarabine) • Trifluradine/ Tipiracil • KTE-X19 • Gilteritinib

• Ifosphamide, carboplatin, etoposide (ICE) • Gemcitabine, dexamethasone, cisplatin (GDP) • Isatuximab • Polatuzumab • Acalabrutinib • Dexamethasone, cytarabine, cisplatin (DHAP) • Etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP) • Cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD) • Dacarbazine-based regimens • Lomustine • Magalizumab • Brentuximab vedotin • Asparaginase-based regimens	

Appendix 3 In-Patient Pathway in NHS GGC and Prescribing Guidance

